Claim 30 stands rejected under 35 USC 101 and 35 USC 112, first paragraph. Cancellation of the claim renders the rejections moot.

Claims 21-24, 26-28, and 30-39 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and for the reasons that follow.

The present invention relates to a method of producing an expression library. A key to the invention is the ability of cis-proteins to covalently bind to their own DNA. Applicants submit that once one of skill in the art is told that an expression library can be produced in this way using cis acting proteins, it would be a matter of routine to use any cis acting protein in the method of the invention. Accordingly, it would be wholly unreasonable to restrict Applicants to the cis acting proteins P2A.

The Examiner refers at the top of page 9 of the Action to the degeneracy of DNA molecules wherein a codon "can encode two or more different residues". Respectfully, as the statement is understood, it is technically inaccurate. The degeneracy of the code means that two different codons can encode the same amino acid. A particular codon, however, only encodes a single amino acid. The Examiner

refers in the same paragraph to the present invention involving the use of polynucleotide amplification techniques. The incorporation of an amplification step, such as PCR, is included in a vast number of applications. The Office clearly does not view the fact that a certain frequency of mutation may occur as rendering unpatentable any and all inventions that include such a step.

The Examiner has argued that only specific screening of a specific library results in a desired compound and that screening is known to be a formidable task for a created library. In the case of the present invention, Applicants are concerned with the creation of the library as such and not the isolation of a selected compound.

In the present instance, the invention derives, at least in part, from the recognition that cis acting proteins can be use in the production of peptide libraries. The proteins make specific use of a characteristic of such cis acting proteins, namely the ability to bind to their own encoding DNA. While the Examiner suggests that it would be not predictable that other cis proteins be used based on the disclosure and examples which demonstrate that a single cis acting protein (namely P2A) could be used. Applicants respectfully disagree. On the contrary, if a protein has the desired cis acting activity, the protein

would be expected to be useful in the method of the present invention. The technical requirement is merely the substitution of DNA encoding such other cis acting protein in place of DNA encoding P2A, as described in the examples.

The Examiner's comment in paragraph 5 at the bottom of page 9 of the Action is not understood and clarification is respectfully requested so that Applicants can respond appropriately.

The Examiner's assertion to the contrary, the present application is not merely an invitation to experiment. Applicants have demonstrated that cis acting proteins, exemplified by P2A, can be used in the production of peptide expression libraries. A declaration will shortly be submitted that demonstrates that it is a straightforward matter to extend the disclosure in relation to P2A to ϕX174 and other cis acting proteins.

In view of the above, reconsideration is requested.

Claims 21-39 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is believed to be in order in view of the above claim amendments and cancellations and comments that follow.

The Examiner contends that the step by which the population of peptides is specifically associated with DNA

is missing. Applicants note, however, that this is an inherent part of the expression process. Cis acting proteins have a specific activity that they bind to their own encoding DNA. This binding occurs during the expression process. Thus, if DNA encoding a cis acting protein is transcribed and translated, the inevitable result is the cis acting protein bound to its own encoding DNA.

The term "ampifiable" does not appear in the claims as now presented.

The terms "derived from" and "a functionally equivalent fragment, variants and derivatives thereof" do not appear in the present claims. The reference to "*in vitro*" in claim 24 is used to describe the situation where the method is carried out in an extracellular environment. It is not necessary to carry out the present invention in a cell or organism as such. This definition of *in vitro* can be understood from the description.

Claim 26 has been amended to read "that does not hybridize to the attachment site".

The revision of claim 31 is believed to address the Examiner's concerns.

The Examiner argues that claim 36 is indefinite. The method effectively relates to assessing the target bound

probe via the reporter moiety. The revision of claim 36 is believed to address the Examiner's concern.

In view of the above, reconsideration is requested.

Claims 21-39 stand rejected under 35 USC 103 as allegedly being obvious over Liu et al, Virology (1996) alone or in view of Mattheakis et al. The rejection is traversed.

In the Materials and Methods section of Liu et al, a number of different mutants are described with a view to elucidating the mechanism of action and function of the P2A protein. There is no suggestion in this document that DNA constructs can be made comprising nucleic acids sequences encoding a display moiety together with nucleic acid sequences encoding the cis acting protein. There is certainly no suggestion in this document that the cis acting protein might in any way be useful in the production of display expression libraries.

As regards Mattheakis et al, the Examiner's attention is directed to the comments offered in the October 9, 2001 Amendment, those comments being incorporated cited herein by reference. It is important to note that Mattheakis et al relates to polysome libraries. In these libraries, P ribosomes are effectively used to link a mRNA molecule with its encoded protein. Such systems are described in general

terms in the background section to the present application. Attached is a review by Dr. FitzGerald (and PTO-1449 Form listing same) setting out the different types of display libraries and also their uses. Some of the key display technologies include phage display, the covalent display technology which is that described in the examples of the present application and the polysome display technology of the sort described by Mattheakis et al.

Given that Mattheakis et al is particularly concerned with the polysome technology, it is not seen that there is any motivation in the document to change to a system that does not require polysomes. There is certainly no motivation in that document to look to the cis acting proteins of the type described by Liu et al. It can only be with hindsight that these documents are combined to reach the claimed invention.

Reconsideration is requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

LINDQVIST et al -- Serial No.: 09/331,808

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

21. (Amended) A method of producing a peptide or protein expression library which displays a population of peptides or proteins, wherein the peptides or proteins are specifically associated with the DNA encoding them through covalent binding of protein to the encoding DNA, said method comprising at least the following steps:

1) preparing a [an amplifiable] genetic library of a population of DNA molecules, each DNA molecule comprising:

(a) a nucleotide sequence encoding a binding moiety comprising an amino acid sequence which is a *cis*-acting DNA binding protein which binds specifically to the DNA encoding sequence through covalent binding of the amino acid sequence to DNA, and

(b) a nucleotide sequence encoding a display moiety comprising an amino acid sequence for display, and wherein the display moiety comprises [has] at least one site of attachment for the binding moiety, and

2) expressing the genetic library thus formed[, to produce] whereby the population of peptides or proteins is produced each specifically associated with and covalently bound to the DNA encoding sequence [them through covalent binding of protein to the encoding DNA].

22. (Amended) The method as claimed in claim 21 [19] wherein expression of the genetic library [material] is performed *in vivo* with at least one copy of a single library member[, optionally present in more than one copy,] expressed per host cell or organism.

24. (Amended) The method as claimed in claim 21 [19] wherein [said amino acid sequence which binds to said encoding sequence is derived from a *cis*-acting protein or functionally-equivalent fragment, variant or derivative thereof and] expression of the genetic library [material] is performed *in vitro*.

25. (Amended) The method as claimed in claim 21 [19] wherein said *cis*-acting protein is the P2 A protein.

26. (Amended) The method as claimed in claim 24 [22] wherein said expression is performed in the presence of a mis-match oligonucleotide which hybridizes to the DNA adjacent to the attachment site on both sides but that does not hybridize [in the region corresponding] to the attachment site.

27. (Amended) The method as claimed in claim 21 [19] wherein said amino acid sequence for display is up to 40 amino acid residues.

28. (Amended) The method as claimed in claim 21 [19] wherein said amino acid sequence for display is generated by, or comprises DNA fragments from, cloning.

29. (Amended) A method as claimed in claim 21 [19] wherein said binding moiety is derived from P2A which has been modified by replacement of tyrosine at amino acid position 450 with phenylalanine.

31. (Amended) A DNA molecule comprising [containing a DNA sequence encoding a peptide or protein for expression in a library according to claim 28, containing] a sequence encoding a binding moiety comprising an amino acid sequence

that is a cis-acting DNA binding protein that binds specifically to the DNA encoding sequence through covalent binding of the amino acid sequence to the DNA, and [which binds specifically to said encoding sequence through covalent protein:DNA binding (binding moiety),] a sequence encoding a display moiety comprising an amino acid sequence for display, the display moiety comprising [(display moiety) and] at least one site of attachment for the binding moiety[, and degenerate and/or functionally equivalent sequences].

32. (Amended) A DNA vector comprising the [containing a] DNA molecule [sequence] as claimed in claim 31 [29].

34. (Amended) A method of identifying a specific target-binding peptide or protein, said method comprising at least the steps of a) screening a peptide expression library produced according to the method of claim 21 [as claimed in claim 28] with a target molecule [molecules] and b) selecting and isolating a library member binding to said target molecule and c) isolating the peptide or protein which binds specifically to said target molecule.

35. (Amended) The method as claimed in claim 34 [32] further comprising isolating [wherein additionally] the DNA sequence encoding [expressing] the peptide or protein that [which] binds specifically to said target molecule [is isolated].

36. (Amended) A method of assaying for the presence of a target molecule in a sample, said method comprising

(a) contacting said sample with a molecular probe comprising

(i) a peptide or protein target-binding moiety capable of selectively binding to said target molecule[, with attached encoding DNA, the DNA moiety, selected from the library as claimed in claim 28] wherein said target-binding moiety is covalently bound to DNA encoding said target binding moiety and

(ii) a reporter moiety[;]

wherein said contacting is effected under conditions such that said target-binding moiety can bind target molecule present in said sample; and

(b) [directly or indirectly assessing the target bound] detecting the presence of reporter moiety bound to said molecular probe.

39. (Amended) The method according to claim 21 [19], wherein said nucleic acid encoding said amino acid sequence for display is generated by amplification by PCR.